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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,716	06/10/2005	Toshiya Fujisato	AKA-0286	6913
23599 7590 05/07/2010 MILLEN, WHITE, ZELANO & BRANIGAN, P.C. 2200 CLARENDON BLVD. SUITE 1400 ARLINGTON, VA 22201				
EXAMINER TON, THAIAN N				
ART UNIT 1632		PAPER NUMBER		
NOTIFICATION DATE 05/07/2010		DELIVERY MODE ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary

Application No.

10/538,716

Applicant(s)

FUJISATO ET AL.

Examiner

Thaia N. Ton

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 March 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 5 and 7-11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 5 and 7-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/22)
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date: _____

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/26/10 has been entered.

Applicants have filed no amendment or response with the request for continued examination. Therefore, the Examiner responds to Applicants arguments, filed with the After-Final Amendment, dated 2/26/10. Claim 10 is amended; claims 5, 7-11 are pending and under current examination.

Claim Rejections - 35 USC § 112

The prior rejection of claims 5, 7-11 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants' amendment to the claims which no longer recites that complete decellularization of the tissue is effected.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 7-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite because the metes and bounds of the claim cannot be ascertained. The term "even in the deep interior portions" in the claim is a relative term which renders the claim indefinite. The term "deep" is not defined by the

claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicants have amended the claims to recite that the tissue is decellularized even in “deep” interior portions. It is unclear how deep into the tissue decellularization would need to occur. Applicants argue that this language does not change the scope of the claims, as much as it represents “complete” decellularization as previously recited (p. 4, 2nd ¶ of the Response). These arguments are not persuasive because the range of how “deep” or how “interior” a portion must be decellularized is not defined by the claim. The term is relative because it does not compare the depth or interior of the tissue to any other tissue with a different depth or interior portion. Furthermore, the phrase that the tissue is decellularized even in the deep interior portions of the tissue is not equivalent language, as asserted by Applicants, “complete” decellularization, because it only refers to decellularization, and does not require complete decellularization. Claims 5, 7-9 and 11 depend from claim 10.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5, 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Login et al (US 4994237, 1991) in further in view of Giberson et al (US 6875583, 2005) and Boon et al (EP0362438A1, 1990).

Applicants' Arguments. Applicants argue that, with regard to the art of Login, they disclose a process employing microwave irradiation along with a physiologic salt solution or dilute aldehyde solution to preserve tissue in preparation of bioprosthesis for implantation into a patient. Applicants argue that OBS, taught by Login, is used to prevent the loss of cellular constituents due to diffusion, which is consistent with "tissue fixing", and that tissue fixing is not decellularization in the deep interior of the tissue (*i.e.*, in a complete manner so as to remove all cells). Applicants argue that treatment or immersion in a solution such as OBS does not enable removal of cellular components, even with the microwave radiation treatment. Applicants argue that Login's methods have a short time (between one and 50 seconds) and do not result in deep interior decellularization. Applicants argue that the instant invention teaches that the tissue immersed in treating solution is irradiated with considerably greater intensity (2450 MHz) for a net period of time so as to achieve complete decellularization. Thus, Applicants argue that the microwave irradiation in claim 10 is at least 72 times that of Login's method, and Login's microwave oven will be automatically shut off when the pre-set final irradiation temperature of the solution is obtained. Applicants argue that Login never irradiates the tissue specimen in OBS with microwave energy at a dose and length of time such that the temperature of the solution reaches above the patentees' preset temperature of 35°-50°C. Applicants argue that the disclosure of Login does not suggest to one of ordinary

skill in the art, particularly in the absence of a decellularizing chemical, complete decellularization and/or the conditions recited in the present invention. Applicants argue that the OBS of Login are free of any decellularizing chemical such as the presently recited detergents, and not capable of decellularization native biological tissues. See pages 4-5 of the Response.

Applicants further argue that the art of Giberson and Boon do not remedy the deficiencies in Login because in Giberson, the tissue specimen is immersed in formalin based solution, which is a fixation chemical. Boon teaches use of alcohol or glutaraldehyde as an immersion chemical, and thus, only teaches fixation and not complete decellularization. See page 5 of the Response.

Response to Arguments. These arguments have been fully considered but are not persuasive. Firstly, Applicants argue limitations that are not found in the claims. The claims do not require complete decellularization, they require that the tissue is decellularized, even in deep interior portions. That is, the tissue must be decellularized, even in the interior of the tissue. This does not require any degree of decellularization, just that decellularization occur.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The Login reference is used as a primary reference, but not used for teachings the specific requirements of time and frequency of the microwave. The art of Giberson and Boon provide guidance for these specific limitations as set forth in the rejection. With regard to OBS, Login teaches various combinations that can be used in their methods, some of which include fixation chemicals, but others which do not (see also, Table 1 and col. 5, lines 20-25). In fact, Login teaches that one of the drawbacks to the standard method of using glutaraldehyde is that it makes the tissue susceptible to tears in the valve, calcification of valve leaflets, and

induces thrombi following implantation (col. 3, lines 26-30) and they teach that their method can use microwave radiation in conjunction with either 1) a physiological salt solution or 2) a dilute aldehyde solution, which leads to a degree of preservation such that tissue flexibility is promoted and collagen cross-linking is minimized. See col. 2, lines 46-51. In particular, Login teaches that the addition of a fixation chemical is optional, but not required.

In response to applicant's argument that the cited art of record is directed to fixing tissues, whereas the instant invention is directed to decellularization of tissue, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In the instant case, the cited art of record provides guidance with regard to the specific solution containing a detergent, the specific temperature, time and microwave frequency range. The cited art of record provides sufficient guidance and motivation to arrive at the claimed invention. If Applicants intend that the decellularization is an unexpected result, the claims must be commensurate in scope to that which provides the unexpected result.

Rejection

Login et al teaches a method to prepare biological tissues (e.g. heart valves, veins, cartilage, ligaments) and organs for use as bioprostheses, and more particularly, it relates to a rapid method to preserve tissue samples with a solution, to irradiate samples in a microwave oven (*Note: standard microwave oven operates at 2.45 GHz see Boon et al EP0362438A1, 1990*), and to store samples in a storage medium (see Fig-1, Spec. col.1, lines 12-20. also Col. 8-10 i.e. claims). The cited art further teaches that microwave irradiation in conjunction with a physiologic salt solution or a dilute aldehyde solution, leads to a degree of preservation such that

tissue flexibility is promoted and collagen cross-linking is minimized. The cited art further teaches that the object of the present invention is to preserve biologic tissue for implantation into animals or humans such that the bioprosthesis will function physiologically (i.e. resist mechanical failure under physiologic conditions). In order to achieve this goal, microwave energy is used to irradiate the tissue (see Spec. col.5, lines 60-). The cited art further teaches that the tissue is immersed in an osmotically balanced solution (OBS, see table-1) and then irradiated in a microwave oven until the OBS reaches a temperature within the range of 35°C to 50°C. The cited art further teaches that after the microwave irradiation, the tissue is transferred and stored in a cold sterile saline solution (see Spec. col. 3, lines 53-68).

The cited art further teaches that the broadest aspects of the invention involve removing the tissue from its blood supply, immersing the tissue in an osmotically balanced solution (OBS) initially at room temperature (approximately 20°C), irradiating the immersed tissue with microwave energy at a sufficient dose and for a sufficient time such that the temperature of the solution is within the range of 35°C. to 50°C, and storing the tissue in a sterile OBS until it is implanted in a patient (see spec col.4, lines 35-45).

The cited art further teaches a comparison study using pig heart valves, wherein the valve leaflets were rinsed in standard electrolyte solution and fixed using three different treatment methods: (a) immersion in a 0.6% glutaraldehyde solution for 24 hours at 25°C. (b) immersion in an aldehyde OBS at 22°C and exposure to microwave irradiation for 11 seconds to reach a final solution temperature of 47°C and (c) immersion in an aldehyde OBS at 22°C. wherein irradiation exposure time was limited to 8 seconds at which time the solution reached a final temperature of 40°C. The cited art teaches that the microwave treated samples were removed from the warm solution within thirty seconds and were stored in 0.9% saline at 4°C with 0.02% sodium azide (see col.6, line 20-).

In addition, if the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. *See In re Casey, 152 USPQ 235 (CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963)*. In the instant case Login et al clearly teaches that the immersed tissue are irradiated with microwave energy at a sufficient dose and for a sufficient time such that the temperature of the solution is within the range of 35°C to 50°C, which would lead to decellularization as claimed (see spec col.4, lines 35-45). Thus given the broadest reasonable interpretation the cited art clearly provides guidance for the invention as claimed.

Even though Login et al teaches a method to preparing tissue using microwave treatment while maintaining the temperature between 0°C to 40°C, the cited art does not that the temperature is maintained via heat-exchange contact with a coolant liquid received in a microwave-transmitting vessel, and wherein said tissue is irradiated with microwaves in a microwave oven (at 2450 MHz) for at least one hour.

Giberson et al (US 6875583, 2005) teaches microwave-treatment of fresh tissue, comprising immersing the tissue in a solution comprising a detergent and heating the immersed tissue using a microwave at a temperature of 4°C to 40°C by pumping the fixation solution through a cooling apparatus which is outside of the microwave oven for 1 hour. Giberson further teaches that the thickest tissues require approximately 60 min of microwave treatment (see fig-1, col. 5, lines 62-67, col. 10-12).

Boon et al (EP0362438A, 1990) teaches microwave treatment of xenogeneic cartilage transplants using standard microwave device that operates at 2.45 GHz. Thus it would have been obvious to one ordinary skilled in the art at the time the instant invention was made to modify the invention of Login et al with Giberson et al by incorporating a heat exchange device that can maintain temperature in the

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range of 0-40°C using a standard microwave device that operates at 2.45 GHz as taught by Boon et al. One would have been motivated to do so to control tissue overheating during microwave treatment. One would have a reasonable expectation of success, since use of microwave irradiation (*using standard microwave ovens that operate at 2.45 GHz*) to treat tissue sample of choice has been routine in the art at time the instant invention was made. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-21 7-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632